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<p>(21) International Application Number: PCT/GB98/01662 (22) International Filing Date: 5 June 1998 (05.06.98) (30) Priority Data: 9712317.8 13 June 1997 (13.06.97) GB (71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): WOOLLVEN, Peter [GB/GB]; Earls Road, Grangemouth, Stirlingshire FK3 8XG (GB). (74) Agents: FAWKES, David, Melville; Intellectual Property Group, Zeneca Specialties, Hexagon House, P.O. Box 42, Blackley, Manchester M9 8ZS (GB) et al.</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	
<p>(54) Title: BIOCIDAL ORGANIC ACID SALTS OF A POLYMERIC BIGUANIDE</p> <p>(57) Abstract</p> <p>A composition comprising a carrier and a polymeric biguanide in the form of its salt with an organic acid containing from 4 to 30 carbon atoms such as poly(hexamethylenebiguanide) stearate.</p>		

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BIOCIDAL ORGANIC ACID SALTS OF A POLYMERIC BIGUANIDE

The present invention relates to organic acid salts of polymeric biguanides, to compositions thereof, and their use as an industrial biocide or in personal care applications.

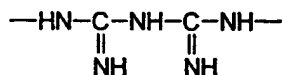
Poly(hexamethylenebiguanide) (hereinafter PHMB) has found many uses as a broad spectrum bactericide in both industrial and personal care applications and is commercially available as an aqueous concentrate of its hydrochloride salt. For most applications, the use of PHMB in the form of its hydrochloride salt is eminently suitable. However, there exist some applications where the presence of chloride ion can cause undesirable side effects such as corrosion of metal surfaces. GB 1,464,005 discloses that other salts of PHMB may be used as molluscicides, such as sulphate, acetate, gluconate and behenate. However, no microbiological data is recorded for such salts. Behenic acid is an aliphatic carboxylic acid containing a C₂₁-alkyl chain and falls within the group, anionic surfactants. The concentrated aqueous solution of PHMB in the form of its hydrochloride salt is clearly stated to be incompatible with anionic surfactants, alkyl sulphonates and anionic caramels as disclosed in the Product Information Notes for Vantocil IB (37-8E dated 1 June 1994) and Cosmocil CQ (37-26E dated 1 April 1994). Both Vantocil and Cosmocil are registered trade marks of Zeneca Specialties.

Bisbiguanides have also been made available commercially as water-soluble salts such as chlorhexidine (1,1'-hexamethylene bis[5-(4-chlorophenyl)-biguanide]digluconate) and alexidine (1,1'-hexamethylene bis [5-(4-(2-ethylhexyl)phenyl)-biguanide]-diacetate). These water-soluble salts and PHMB hydrochloride are not particularly suited to provide a solution of the polymeric biguanide in organic liquids, especially non-polar organic liquids.

It has now been found that PHMB in the form of its salt of an organic acid containing from 4 to 30 carbon atoms exhibits high antimicrobial, especially antibacterial activity, and that such salts exhibit increased solubility in organic media, especially organic liquids.

According to the present invention there is provided a composition comprising a carrier and a polymeric biguanide in the form of its salt with an organic acid containing from 4 to 30 carbon atoms, including mixtures thereof.

The polymeric biguanide contains at least one biguanide unit of Formula 1.

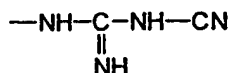


Formula 1

Preferably, the polymeric biguanide contains at least two biguanide units of Formula 1 which are linked by a bridging group which contains at least one methylene group. The bridging group may include a polymethylene chain which may optionally be

interrupted by hetero atoms such as oxygen, sulphur or nitrogen. The bridging group may include one or more cyclic nuclei which may be saturated or unsaturated. Preferably, the bridging group is such that there are at least three, and especially at least four, carbon atoms directly interposed between two adjacent biguanide units of Formula 1. Preferably, there are not greater than ten and especially not greater than eight carbon atoms interposed between two adjacent biguanide units of Formula 1.

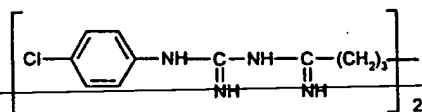
The polymeric biguanide may be terminated by any suitable group which may be a hydrocarbyl or substituted hydrocarbyl group or an amine or a group



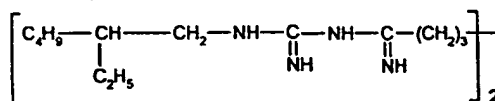
When the terminating group is a hydrocarbyl group, it may be alkyl, cycloalkyl or aralkyl.

When the terminating group is a substituted hydrocarbyl group, the substituent may be any substituent that does not exhibit an undesirable adverse effect on the microbiological properties of the polymeric biguanide. Examples of such substituents or substituted hydrocarbyl groups are aryloxy, alkoxy, acyl, acyloxy, halogen and nitrile.

When the polymeric biguanide contains two biguanide groups of Formula 1, the two biguanide units are preferably linked by a polymethylene group, especially a hexamethylene group. The terminating groups in such polymeric biguanides are preferably 4-chlorophenyl or 2-ethylhexyl. Examples of such compounds are represented by Formulae 2 and 3 in their free base form

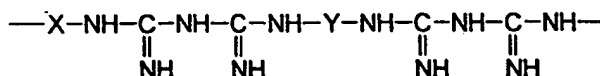


Formula 2



Formula 3

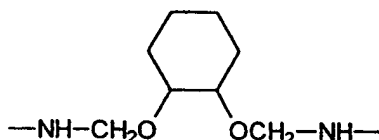
The polymeric biguanide preferably contains more than two biguanide units of Formula 1 and preferably is a linear polymeric biguanide which has a recurring polymeric unit represented by Formula 4



Formula 4

wherein X and Y may be the same or different and represent bridging groups in which, together, the total number of carbon atoms directly interposed between the pairs of nitrogen atoms linked by X and Y is not less than 9 and not greater than 17.

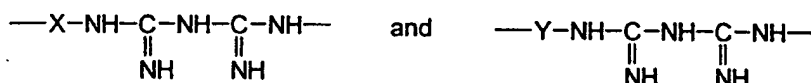
The bridging groups X and Y may consist of a polymethylene chain, optionally interrupted by a heteroatom such as oxygen, sulphur or nitrogen. X and Y may also incorporate a cyclic nucleus which may be saturated or unsaturated, wherein the number of carbon atoms directly interposed between the pairs of nitrogen atoms linked by X and Y is taken as including that segment of the cyclic group, or groups, which is the shortest. Thus, the number of carbon atoms directly interposed between the nitrogen atoms in the group



is 4 and not 8.

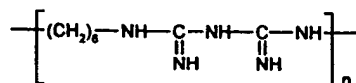
The preferred polymeric biguanide for use in the present invention is poly(hexamethylenebiguanide), in which both X and Y in Formula 4 are the group $-(CH_2)_6-$

The polymeric biguanides of Formula 4 are typically obtained as mixtures of polymers in which the polymer chains are of different lengths. Preferably, the number of individual biguanide units



is, together, from 3 to about 80.

In the case of the preferred poly(hexamethylenebiguanide) it is a mixture represented by the compounds of Formula 5 in the free-base form.



Formula 5

wherein the value of n is from 4 to 40 and especially from 4 to 15. It is particularly preferred that the average value of n in the mixture is 12. Preferably, the average molecular weight of the polymer mixture is from 1100 to 3300.

The organic acid which forms the salt with the polymeric biguanide may contain a phosphonic, phosphoric, sulphonic or sulphate group but preferably contains a carboxylic acid group. The organic acid may be aromatic but is preferably aliphatic, including alicyclic. When the organic acid is aliphatic, the aliphatic chain of the organic acid may be linear or branched, saturated or unsaturated, including mixtures thereof. Preferably, the

aliphatic chain is linear and it is also preferred that the organic acid is an aliphatic carboxylic acid.

It is preferred that the organic acid contains not less than eight, more preferably not less than ten and especially not less than twelve carbon atoms excluding the acid group. Preferably, the organic acid contains not greater than 24, more preferably not greater than 20 and especially not greater than 18 carbon atoms excluding the acid group.

The organic acid may contain more than one acid group but it is preferred that only one such group is present.

The organic acid may be substituted by a halogen or particularly hydroxy group. It is, however, preferred that the organic acid is free from substituents.

Some aliphatic carboxylic acids are available commercially as mixtures such as those obtained from animal fats and vegetable oils and these contain both saturated and unsaturated aliphatic chains. These have also been found useful, especially the C_{14-18} -alkyl carboxylic acids and their fully saturated or hydrogenated analogues.

Examples of optionally substituted carboxylic acids are valeric, hexanoic, octanoic, 2-octenoic, lauric, 5-dodecanoic, myristic, pentadecanoic, palmitic, oleic, stearic, eicosanoic, heptadecanoic, palmitoleic, ricinoleic, 12-hydroxystearic, 16-hydroxyhexadecanoic, 2-hydroxycaproic, 12-hydroxydodecanoic, 5-hydroxydodecanoic, 5-hydroxydecanoic, 4-hydroxydecanoic, dodecanedioic, undecanedioic, sebacic, benzoic, hydroxybenzoic and teraphthalic acids.

Particularly useful effects have been obtained when the aliphatic carboxylic acid is stearic acid and the polymeric biguanide is PHMB.

The carrier may be a solid but is preferably a liquid.

The liquid may be water whereby the composition containing the organic acid is a dispersion or emulsion. Preferably, the aqueous composition also contains a surfactant, particularly a non-ionic surfactant such as a polyalkylene oxide and especially an ethoxylate. The aqueous composition may also contain other adjuvants which help distribute the polymeric biguanide salt uniformly throughout the composition. Examples of such adjuvants are compounds which provide structure to the water to inhibit sedimentation such as alginates and gums, particularly Xanthan gum.

When the carrier is a liquid it is preferably a polar organic liquid, a substantially non-polar organic liquid or a halogenated hydrocarbon. By the term "polar" in relation to the organic liquid is meant an organic liquid or resin capable of forming moderate to strong bonds as described in the article entitled "A Three Dimensional Approach to Solubility" by Crowley et al in Journal of Paint Technology, Vol. 38, 1966, at page 269. Such organic liquids generally have a hydrogen bonding number of 5 or more as defined in the above mentioned article.

Examples of suitable polar organic liquids are amines, ethers, especially lower alkyl ethers, organic acids, esters, ketones, glycols, alcohols and amides. Numerous specific examples of such moderately strongly hydrogen bonding liquids are given in the book entitled "Compatibility and Solubility" by Ibert Mellan (published in 1968 by Noyes Development Corporation) in Table 2.14 on pages 39-40 and these liquids all fall within the scope of the term polar organic liquid as used herein.

Preferred polar organic liquids are dialkyl ketones, alkyl esters of alkane carboxylic acids and alkanols, especially such liquids containing up to, and including, a total of 6 carbon atoms. As examples of the preferred and especially preferred liquids there may be mentioned dialkyl and cycloalkyl ketones, such as acetone, methyl ethyl ketone, diethyl ketone, di-isopropyl ketone, methyl isobutyl ketone, di-isobutyl ketone, methyl isoamyl ketone, methyl n-amyl ketone and cyclohexanone; alkyl esters such as methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate, ethyl formate, methyl propionate, methoxy propylacetate and ethyl butyrate; glycols and glycol esters and ethers, such as ethylene glycol, 2-ethoxyethanol, 3-methoxypropylpropanol, 3-ethoxypropylpropanol, 2-butoxyethyl acetate, 3-methoxypropyl acetate, 3-ethoxypropyl acetate and 2-ethoxyethyl acetate; alkanols such as methanol, ethanol, n-propanol, isopropanol, n-butanol and isobutanol and dialkyl and cyclic ethers such as diethyl ether and tetrahydrofuran.

The substantially non-polar, organic liquids which may be used, either alone or in admixture with the aforementioned polar liquids, are aliphatic and aromatic hydrocarbons, such as toluene and xylene, and halogenated aliphatic and aromatic hydrocarbons, such as trichloro-ethylene, perchloroethylene and chlorobenzene.

The organic acid salt of the polymeric biguanide may be made by any method known to the art but is preferably made by precipitation of the biguanide from aqueous solution by addition of the organic acid under alkaline conditions. The organic acid salts of the biguanide may be further purified by dissolution in a suitable organic liquid which is preferably immiscible with water and washing the organic phase with water to remove any residual water soluble salts.

The amount of polymeric biguanide in the composition may vary between wide limits depending on its end usage. Thus, where the composition is used to confer antimicrobial protection to a medium which is to be protected against microbiological spoilage the amount of polymeric biguanide may be just sufficient to provide such protection. Preferably the amount of biguanide is not less than 1 ppm, more preferably not less than 10 ppm and especially not less than 20 ppm. It will be appreciated that where the composition containing the salt of the polymeric biguanide is to be transported in bulk the amount of the polymeric biguanide salt is as high as possible provided that the biguanide salt remains uniformly distributed throughout the composition. Preferably, the amount of polymeric biguanide salt in the composition is not greater than 30%, more

preferably not greater than 25% and especially not greater than 20% based on the total weight of the composition.

Some of the polymeric biguanides in the form of a salt with an organic acid containing from 4 to 30 carbon atoms are novel. Thus, according to a further aspect of the invention there is provided a polymeric biguanide in the form of a salt with an aliphatic carboxylic acid containing from 4 to 20 carbon atoms, particularly from 10 to 20 carbon atoms and especially from 12 to 18 carbon atoms excluding the -COOH group, optionally substituted by hydroxy.

It is particularly preferred that the aliphatic carboxylic acid is free from substituents.

The aliphatic carboxylic acid may be linear or branched, saturated or unsaturated, including mixtures thereof. It is preferred that the aliphatic carboxylic acid is linear and saturated.

It is especially preferred that the polymeric biguanide is PHMB.

As noted hereinbefore, the organic acid salts of the polymeric biguanide exhibit antimicrobial, especially antibacterial, activity. Consequently, the polymeric biguanide salts or compositions containing the polymeric biguanide salts may be used to protect various media from microbiological growth.

According to a still further aspect of the invention there is provided a method for inhibiting microbiological growth on, or in a medium which comprises treating the medium with a polymeric biguanide in the form of its salt with an organic acid containing from 4 to 30 carbon atoms. The polymeric biguanide salt can be used in any conditions in which micro-organisms grow and cause problems. Thus, the medium may be an industrial medium such as a cooling water tower liquid, paper mill liquor, metal working fluid, geological drilling lubricant, polymer emulsion, surface coating composition such as paint, varnish or lacquer. The medium to be protected can be a solid such as wood or leather and particularly solid surfaces in the health-care or food preparation industries. The solid may also be a textile material such as cellulose, including its blends with synthetic polymers and also non-woven materials such as those used in disposable items such as nappies, incontinence pads and feminine hygiene packs.

Where the medium to be protected is a solid, the polymeric biguanide salt may be applied by any method known to the art such as spraying, dipping or coating with a composition containing the polymeric biguanide salt.

As noted hereinbefore, the amount of polymeric biguanide salt which is applied to the medium to be protected from microbiological growth may be just sufficient to inhibit such growth or it may be in excess of such amount. Preferably, the amount of polymeric biguanide salt which is applied to such medium is not greater than 2% and more preferably not greater than 1% by weight of the medium. Generally, adequate protection

is provided by from 1 ppm to 500 ppm, particularly 10 to 200 ppm and especially 10 to 100 ppm of the polymeric biguanide salt relating to the medium.

The invention is illustrated by the following examples wherein all parts and percentages are references to weight unless indicated to the contrary.

Example 1

Preparation of stearate salt of PHMB

Water (150 litres) was added to a reactor vessel followed by stearic acid (14.8 Kgm, 0.047M). Sodium hydroxide flake (1.88 Kgm, 0.047M) was added with stirring, giving a pH value in the range 9.0 to 10.0. PHMB hydrochloride (50 litres as 20% aqueous solution, 0.047M, Vantocil IB ex. Zeneca) was added and the reactants stirred at 80°C for 2 hours. After cooling, the PHMB stearate salt was separated on a slurry filter, washed with water and dried.

The product was obtained as a paste containing 11.0 Kgm PHMB stearate (50% theory).

The PHMB stearate salt exhibited similar microbiological activity to the hydrochloride salt when allowance is made for the different molecular weights.

Example 2

Palmitic acid (1.35 parts ex Aldrich) were dissolved in water (15ml) by heating to 60°C and adjusting the pH value to between 9 and 10 by adding caustic soda. PHMB hydrochloride (1 part as 20% solution, Cosmocil CQ ex Zeneca) was added and the reactants stirred at 80°C for 2 hours. The reaction mass was then cooled to 20°C whereupon the PHMB palmitate separated as a clear gum (1.86 parts).

Examples 3 and 4

Example 2 was repeated except replacing the palmitic acid with an equivalent amount of lauric acid and octanoic acid, respectively.

Examples 5 to 11

The MIC values for the different salts of poly(hexamethylene biguanide) were determined by dissolving the salts in methanol/dimethylformamide (1:6). The results are given in Table 1 below and show that the different salts exhibit similar antimicrobial activity against yeast and bacteria.

Table 1

Example	Anion	C.albicans	E.coli	St.aureus
5	stearate	100	2.3	3.1
6	palmitate	150	4.7	4.7
7	octanoate	>150	0.8	2.3
8	laurate	>150	1.2	1.2
9	chloride (D)	>150	0.8	1.2
10	chloride (W)	>150	0.4	1.6
11	stearate (M)	>150	2.3	3.1

Foot note to Table 1

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C. albicans is Candida albicans

E. coli is Escherichia coli

St. aureus is Staphylococcus aureus

D. is dried sample of poly(hexamethylenebiguanide) hydrochloride

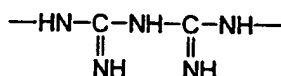
10 W. is sample of poly(hexamethylenebiguanide)hydrochloride dissolved in water

M. is sample of poly(hexamethylenebiguanide)hydrochloride dissolved in methanol.

CLAIMS

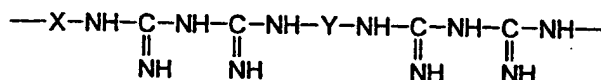
1. A composition comprising a carrier and a polymeric biguanide in the form of its salt with an organic acid containing from 4 to 30 carbon atoms, including mixtures thereof.

2. A composition as claimed in claim 1 wherein the polymeric biguanide contains at least one biguanide unit of Formula 1



Formula 1

3. A composition as claimed in either claim 1 or claim 2 wherein the polymeric biguanide is a linear polymeric biguanide which has a recurring polymeric unit represented by Formula 4

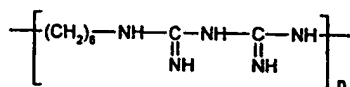


Formula 4

wherein X and Y may be the same or different and represent bridging groups in which together, the total number of carbon atoms directly interposed between the pairs of nitrogen atoms linked by X and Y is not less than 9 and not greater than 17.

4. A composition as claimed in claim 3 wherein both X and Y is the group $-(\text{CH}_2)_6-$.

5. A composition as claimed in any one of claims 1 to 4 wherein the polymeric biguanide is a mixture represented by the compounds of Formula 5 in the free-base form



Formula 5

wherein n is from 4 to 40.

6. A composition as claimed in any one of claims 1 to 5 wherein the organic acid contains a carboxylic acid group.

7. A composition as claimed in any one of claims 1 to 6 wherein the organic acid contains from 12 to 18 carbon atoms.

8. A composition as claimed in any one of claims 1 to 6 wherein the organic acid is selected from valeric, hexanoic, octanoic, 2-octenoic, lauric, 5-dodecenoic, myristic, pentadecanoic, palmitic, oleic, stearic, eicosanoic, heptadecanoic, palmitoleic, ricinoleic, 12-hydroxystearic, 16-hydroxyhexadecanoic, 2-hydroxycaproic, 12-hydroxydodecanoic, 5-hydroxydodecanoic, 5-hydroxydecanoic, 4-hydroxydecanoic, dodecanedioic, undecanedioic, sebacic, benzoic, hydroxybenzoic and terephthalic acids.

9. A composition as claimed in any one of claims 1 to 8 wherein the carrier is a polar organic liquid, a substantially non-polar organic liquid or a halogenated hydrocarbon.

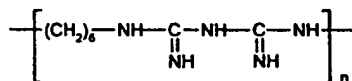
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10. A composition as claimed in claim 9 wherein the polar organic liquid is an alkanol.

11. A polymeric biguanide in the form of its salt with an aliphatic carboxylic acid containing from 4 to 20 carbon atoms excluding the acid group.

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12. The salt of a polymeric biguanide as claimed in claim 11 wherein the polymeric biguanide is a mixture represented by the compounds of Formula 5 in the free-base form



Formula 5

20 wherein n is from 4 to 40.

~~13. The salt of a polymeric biguanide as claimed in either claim 11 or claim 12 wherein the aliphatic acid is stearic acid.~~

25 14. A method for inhibiting microbiological growth on, or in a medium which comprises treating the medium with a polymeric biguanide in the form of its salt with an organic acid containing from 4 to 30 carbon atoms.

Internet Application No
PCT/GB 98/01662

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 434 040 A (ICI LTD) 28 April 1976 see claims see page 5, line 26 - line 39 see page 28	1-14
X	BE 698 595 A (ICI) 17 November 1967 see claims 6,7	1-14
X	GB 843 676 A (ICI) 10 August 1960 see claims	1,2, 6-11,13, 14
X	WO 95 26134 A (UNIV COLUMBIA ;MODAK SHANTA M (US); SAMPATH LESTER A (US); ADVANI) 5 October 1995 see claim 6	1,2, 6-11,14

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

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